HH

03CO #9

Patent
261/011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1631
Michael J. Heller et al.	Examiner: Marschel
Serial No.: 09/912,014	
Filed: July 24, 2001	
For: Methods for Electronic Synthesis of Complex Structures	

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS, SECOND SUPPLEMENTAL PRELIMINARY AMENDMENT, OR IN THE ALTERNATIVE, PETITION FOR ACCEPTANCE OF OMITTED PAGES

Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the application as follows:

In the Specification:

Please amend the specification as noted below. Please note that substitute pages are attached to the end of this document, under tab "Omitted Pages".

Please add the following text at page 37, line 1:

gel provides primary amine functional groups for the subsequent attachment of specific binding entities. This type of gel permeation layer allows the electrodes to function actively in the DC mode.

OC-96895.1

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.

Denise N. Doss
Name of Person Mailing Paper

November 13, 2001
Date of Deposit

Signature of Person Mailing Paper

When the electrode is activated, the gel permeation layer allows small counter-ions to pass through it, but the larger specific binding entity molecules are concentrated on the outer surface. Here they become covalently bonded to the outer layer of primary amines, which effectively becomes the attachment layer.

An alternative technique for the formation of the permeation and attachment layers is to incorporate into the base of each micro-location chamber, a porous membrane material. The outer surface of the membrane is then derivatized with chemical functional groups to form the attachment layer. Appropriate techniques and materials for carrying out this approach are known to those skilled in

the art.

The above descriptions for the design and fabrication of both the microlithographic and micromachined devices should not be considered as a limit to other variations or forms of the basic device. Many variations of the device with larger or smaller numbers of addressable micro-locations or combinations of devices can be for different analytical and preparative applications. Variations of the device with larger addressable locations can be designed for preparative biopolymer synthesis applications, sample preparation, cell sorting systems, in-situ hybridization, reagent dispensers, strong storage systems and waste disposal systems.

II. SELF-DIRECTED ADDRESSING OF THE DEVICES

Please add the following text at page 61, line 1:

The following oligomers contain 5'-amino termini:

ET-21A	5'-Amino-TGC GAG CTG CAG TCA GAC AT
ET-10AL	5'-Amino-GAG AGA CTC ATG AGC AGG
ET-11AL	5'-Amino-CCT GCT CAT GAG TCT CTC
T-2	5'-Amino-TTT TTT TTT TTT TTT TTT T
RC-A1	5'-Amino-CAG GCA GTC TCC TTC CTC TCC AGG TCC ACG TAG
RC-A2	5'-Amino-CTC CAA ATT TGC TGA ACT C
RC-A3	5'-Amino-GGA GAT GAG GAG TTC TAC G
RC-A4	5'-Amino-CTG GAG AGG AAG GAG AC
RC-A5	5'-Amino-CCA CGT AGA ACT GCT CAT C
RC-A6	5'-Amino-GTC TCC TTC TTC TCC AG
RC-A7	5'-Amino-GTC AAA TCT AAG TCT GTG GAA
RC-A8	5'-Amino-ATC TTC TAA ATC TGC GGA A
RC-A9	5'-Amino-GTC TGA GAA CAG GCA AAC A
RC-A10	5'-Amino-ATG TTT TGT CAC AGC GAT G

EXAMPLE 2: Electronically Addressable Micro-locations on a Microfabricated Device - Polylysine Method

The micro-locations were fabricated from microcapillary tubes (0.2 mm x 5 mm). The microcapillaries were filled with 18-26% polyacrylamide containing 0.1 - 1.0% polylysine and allowed to polymerize. The excess capillary was scored and removed to prevent air bubbles from being trapped within the tubes and to standardize the tube length. The capillaries were mounted in a manner such that they shared a common upper buffer reservoir and had individual lower buffer reservoirs. Each lower buffer reservoir contained a platinum wire electrode.

The top surface of the microcapillary in the upper reservoir was considered to be the addressable micro-location. The upper and lower reservoirs were filled with 0.1 M sodium phosphate, pH 7.4 and prerun for 10 minutes

transmittal postcard indicated the application was filed with 103 pages of description, which is in fact the correct number. The postcard was returned with the USPTO date stamp of July 24, 2001. Further, the undersigned has confirmed that the current case in its file did include the four pages in question. The copying machine utilized to make the copies has an automatic feeder. The machine is relatively new (certainly less than one year old). While the undersigned has not been aware of problems with the feeding system, it is possible that the pages were not reproduced. One other copy having the omitted pages has also been found. The copier utilizes a single scan to make multiple copies, which would be consistent with the pages not having been scanned. This having been said, the undersigned does not know whether or not the pages were it the application, and if not, why they were not included. The undersigned can state that the parent case in the file did include the four pages, and it was the intention of the undersigned to include the pages. In conclusion, in the event that the Preliminary Amendment is not effective in adding the four pages, the undersigned would request that the Petition be granted and the pages added.

The Commissioner is hereby authorized to charge any fees necessary with this submission to to Deposit Account No. 12-2475.

Attached hereto is a marked-up version of the changes made to the claims by the currer amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

LYON & LYON LLP

By: David Bly
David Murphy
Reg. No. 31,125

Dated: November 13, 2001

DBM/dnd
633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
(949) 567-2300 or (213) 489-1600

"Version with markings to show changes made"

In the Specification:

The following text has been added at page 37, line 1:

gel provides primary amine functional groups for the subsequent attachment of specific binding entities. This type of gel permeation layer allows the electrodes to function actively in the DC mode. When the electrode is activated, the gel permeation layer allows small counter-ions to pass through it, but the larger specific binding entity molecules are concentrated on the outer surface. Here they become covalently bonded to the outer layer of primary amines, which effectively becomes the attachment layer.

An alternative technique for the formation of the permeation and attachment layers is to incorporate into the base of each micro-location chamber, a porous membrane material. The outer surface of the membrane is then derivatized with chemical functional groups to form the attachment layer. Appropriate techniques and materials for carrying out this approach are known to those skilled in

the art.

The above descriptions for the design and fabrication of both the microlithographic and micromachined devices should not be considered as a limit to other variations or forms of the basic device. Many variations of the device with larger or smaller numbers of addressable micro-locations or combinations of devices can be for different analytical and preparative applications. Variations of the device with larger addressable locations can be designed for preparative biopolymer synthesis applications, sample preparation, cell sorting systems, in-situ hybridization, reagent dispensers, strong storage systems and waste disposal systems.

II. SELF-DIRECTED ADDRESSING OF THE DEVICES

Please add the following text at page 61, line 1:

The following oligomers contain 5'-amino termini:

ET-21A 5'-Amino-TGC GAG CTG CAG TCA GAC AT

ET-10AL 5'-Amino-GAG AGA CTC ATG AGC AGG

ET-11AL 5'-Amino-CCT GCT CAT GAG TCT CTC

T-2 5'-Amino-TTT TTT TTT TTT TTT TTT T

RC-A1 5'-Amino-CAG GCA GTC TCC TTC CTC TCC AGG TCC ACG TAG

RC-A2 5'-Amino-CTC CAA ATT TGC TGA ACT C

RC-A3 5'-Amino-GGA GAT GAG GAG TTC TAC G

RC-A4 5'-Amino-CTG GAG AGG AAG GAG AC

RC-A5 5'-Amino-CCA CGT AGA ACT GCT CAT C

RC-A6 5'-Amino-GTC TCC TTC TTC TCC AG

RC-A7 5'-Amino-GTC AAA TCT AAG TCT GTG GAA

RC-A8 5'-Amino-ATC TTC TAA ATC TGC GGA A

RC-A9 5'-Amino-GTC TGA GAA CAG GCA AAC A

RC-A10 5'-Amino-ATG TTT TGT CAC AGC GAT G

EXAMPLE 2: Electronically Addressable Micro-locations on a Microfabricated Device - Polylysine Method

The micro-locations were fabricated from microcapillary tubes (0.2 mm x 5 mm). The microcapillaries were filled with 18-26% polyacrylamide containing 0.1 - 1.0% polylysine and allowed to polymerize. The excess capillary was scored and removed to prevent air bubbles from being trapped within the tubes and to standardize the tube length. The capillaries were mounted in a manner such that they shared a common upper buffer reservoir and had individual lower buffer reservoirs. Each lower buffer reservoir contained a platinum wire electrode.

The top surface of the microcapillary in the upper reservoir was considered to be the addressable micro-location. The upper and lower reservoirs were filled with 0.1 M sodium phosphate, pH 7.4 and prerun for 10 minutes

Please add the following text at page 85, line 1:

The particles are stored as a 2% suspension in distilled water. An aliquot of 25 to 50 µl of the 0.02 - 1.0 µm amine modified red fluorescent fluorospheres was pelleted and re-suspended in 0.1M sodium phosphate, pH 7.4. An excess of periodate oxidized poly ribo-A was added to the suspension. The reaction was allowed to incubate for 90 minutes at room temperature. The particles were washed and pelleted several times in 1x SSC, 0.1% SDS (0.15 mM sodium chloride, 0.015 mM sodium citrate, 0.1% (w/v) sodium docecyl sulfate, pH 7.0) to remove unbound and nonspecifically bound poly ribo-A.

The DNA-fluorospheres in buffered solution were placed in a direct current electric field. It was observed that the DNA-Fluorospheres migrated towards the positive electrode,

fragments can now be transported to the secondary DNA or restriction fragment selector unit by biasing it positive. This unit is designed to selectively bind large fragments of DNA, using appropriate capture sequences on its surface.

At this point, selected DNA fragments can be transported to the APEX analytical chip for hybridization analysis. It is also possible to transport DNA fragments to the storage unit or even out of the system. The examples above represent just some of the possible scenarios for sample preparation and multiple hybridization analysis. The binding affinity programmability of components and flexibility of combining different components and functions allows a wide variety of procedures to be carried out.

While DNA is used as a primary example, the above described device and method can also be used for the

Patent
26/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:	Group Art Unit: 1631
Michael J. Heller et al.	Examiner: Marschel
Serial No.: 09/912,014	
Filed: July 24, 2001	
For: Methods for Electronic Synthesis of Complex Structures	

SUPPLEMENTAL PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the application as follows:

IN THE SPECIFICATION:

At page 10, line 25, delete "claimed".

At page 10, line 29, delete "claimed".

At page 12, line 17, delete "claimed" and insert therefor --disclosed--.

At page 12, line 23, delete "claimed" and insert therefor --disclosed--.

At page 19, line 15, delete "which was actually fabricated, addressed with oligonucleotides, and tested".

OC-91407.1

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as First Class Mail in an envelope addressed to the Commissioner for Patents, Washington, D.C. 20231.

Denise N. Doss
Name of Person Mailing Paper

Signature of Person Mailing Paper

September 21, 2001
Date of Deposit

At page 19, line 25, delete "Figure 7 shows" and insert therefor --Fig. 7a and Fig. 7b show--.

At page 19, line 27, after "micro-location" insert --, Fig. 7a showing the addressable microlocations in a neutral condition and Fig. 7b showing the addressable microlocations in a charged state--.

At page 19, line 28, delete "Figure 8 shows" and insert therefor --Figs. 8a, 8b, 8c and 8d show--.

At page 19, line 30, after "SSO-C)" insert --, Fig. 8a showing a first microlocation (ML-1) being addressed, Fig. 8b showing a second microlocation (ML-2) being addressed, Figure 8c showing a third microlocation (ML-3) being addressed and Figure 8d showing the three microlocations after being addressed and assembled--.

At page 19, line 31, delete "Figure 9 shows" and insert therefor --Figs. 9a, 9b and 9c show--.

At page 20, line 2, after "capture sequences" insert --, Fig. 9a showing specific capture sequences on addressable microlocations, Fig. 9b showing specific and nonspecific DNA adjacent the structure of Fig. 9a, and Fig. 9c showing hybridized material adjacent microlocations ML-1 and ML-3--.

At page 20, line 3, delete "Figure 10 shows" and insert therefor --Figs. 10a and 10b show--.

At page 20, line 4, after "hybridization process" insert --, Fig. 10a showing materials adjacent microlocation ML-3 and Fig. 10b showing materials adjacent microlocations ML-3 and ML-5--.

At page 20, line 5, delete "Figure 11 shows" and insert therefor --Figs. 11a, 11b and 11c show--.

At page 20, line 7, after "mutations" insert --, Fig. 11a showing uncharged addressable microlocations, Fig. 11b showing negatively charged microlocations and Fig. 11c showing negatively charged microlocations with material denatured from microlocation ML-3--.

At page 20, line 8, delete "Figure 12 shows" and insert therefor --Figs. 12a, 12b, 12c and 12d show--.

At page 20, line 11, after "process" insert --, Fig. 12a showing uncharged microlocations, Fig. 12b showing negatively charged microlocations, Fig. 12c showing uncharged microlocations with dye and Fig. 12d showing positively charged microlocations--.

At page 20, line 12, delete "Figure 13 shows" and insert therefor --Figs. 13a, 13b and 13c show--.

At page 20, line 13, after "device" insert --, Fig. 13a showing negatively charged addressable microlocations, Fig. 13b showing two opposed substrates, one substrate being that of Fig. 13a and the other being a sister device containing an attachment layer, and Fig. 13c showing two substrates, each of which has sequences bound to the microlocations--.

At page 20, line 14, delete "Figure 14 shows" and insert therefor --Figs. 14a, 14b, 14c, 14d, 14e, and 14f show--.

At page 20, line 15, after "oligonucleotides" insert --, Fig. 14a showing addressable microlocations with blocking groups, Fig. 14b showing addressable microlocations with blocking groups in combination with a deblocking group, Fig. 14c showing blocked and deblocked addressable microlocations in the presence of monomer C, Fig. 14d showing addressable microlocations in combination with a deblocking group, Fig. 14e showing deblocked cites on microlocation ML-2 in the presence of monomer A and Fig. 14f showing microlocations with blocking groups on the terminal ends of sequences--.

At page 39, line 15, delete "Figure 7" and insert therefor --Figs. 7a and 7b--.

At page 39, line 21, delete "Figure 8" and insert therefor --Figs. 8a through 8d

At page 42, line 1, delete "claimed".

At page 42, line 18, delete "claimed" and insert therefor --disclosed--.

At page 43, line 12, delete "Figure 8" and insert therefor --Figs. 8a through 8d--.

At page 44, line 27, delete "Figure 9" and insert therefore --Figs. 9a through 9c--.

At page 45, line 24, delete "Figure 10" and insert therefor --Figs. 10a and 10b--.

At page 46, line 4, delete "claimed" and insert therefor --disclosed--.

At page 46, line 8, delete "Figure 11" and insert therefor --Figs. 11a through 11c--.

At page 49, line 1, delete "Figure 12" and insert therefor --Figs. 12a through 12d--.

At page 51, line 7, delete "Figure 13" and insert therefor --Figs. 13a through 13c--.

At page 54, line 12, "Figure 14" and insert therefor --Figs. 14a through 14f--.

At page 60, line 7, after "TCU" insert --(Sequence No. 1)--.

At page 60, line 8, after "AAU" insert --(Sequence No. 2)--.

At page 60, line 9, after "CTG U" insert --(Sequence No. 3)--.

At page 60, line 10, after "GU" insert --(Sequence No. 4)--.

At page 60, line 11, after "CU" insert --(Sequence No. 5)--.

At page 60, line 12, after "AGU" insert --(Sequence No. 6)--.

At page 60, line 13, after "GU" insert --(Sequence No. 7)--.

At page 60, line 14, after "ACU" insert --(Sequence No. 8)--.

At page 60, line 15, after "GAC U" insert --(Sequence No. 9)--.

At page 60, line 16, after "TU" insert --(Sequence No. 10)--.

At page 60, line 17, after "CU" insert --(Sequence No. 11)--.

At page 60, line 18, after "TU" insert --(Sequence No. 12)--.

At page 61, line 2, after "AT" insert --(Sequence No. 13)--.

At page 61, line 3, after "AGG" insert --(Sequence No. 14)--.

At page 61, line 4, after "CTC" insert --(Sequence No. 15)--.

At page 61, line 5, after "TTT T" insert --(Sequence No. 16)--.

At page 61, line 7, after "TAG" insert --(Sequence No. 17)--.

At page 61, line 8, after "ACT C" insert --(Sequence No. 18)--.

At page 61, line 9, after "TAC G" insert --(Sequence No. 19)--.

At page 61, line 10, after "AC" insert --(Sequence No. 20)--.

At page 61, line 11, after "CAT C" insert --(Sequence No. 21)--.

At page 61, line 12, after "AG" insert --(Sequence No. 22)--.

At page 61, line 13, after "GAA" insert --(Sequence No. 23)--.

At page 61, line 14, after "GGA A" insert --(Sequence No. 24)--.

At page 61, line 15, after "AAC A" insert --(Sequence No. 25)--.

At page 61, line 16, after "GAT G" insert --(Sequence No. 26)--.

At page 70, line 8, delete "the".

At page 71, line 10, delete "silica" and insert therefor --silicon--.

At page 71, line 28, delete ". Then" and insert therefor --, and then--

At page 75, line 33, after "micro-location" insert --(Sequence No. 27)--.

At page 76, line 2, after "micro-location" insert --(Sequence No. 28)--.

At page 76, line 5, after "(TR)" insert --(Sequence No. 29)--.

At page 76, line 6, after "(TR)" insert --(Sequence No. 30)--.

At page 76, line 7, after "(TR)" insert --(Sequence No. 31)--.

At page 78, line 12, after "GAU" insert --(Sequence No. 32)--.

At page 78, line 14, after "GA" insert --(Sequence No. 33)--.

At page 78, line 15, after "CCA C" insert --(Sequence No. 34)--.

At page 78, line 16, after "CCA C" insert --(Sequence No. 35)--.

At page 78, line 17, after "CCA C" insert --(Sequence No. 36)--.

At page 78, line 18, after "CCG C" insert --(Sequence No. 37)--.

At page 78, line 19, after "ACG C" insert --(Sequence No. 38)--.

At page 89, line 4, after "CAG U" insert --(Sequence No. 39)--.

At page 89, line 5, after "GTG U" insert --(Sequence No. 40)--.

At page 89, line 7, after "ACC G" insert --(Sequence No. 41)--.

At page 89, line 9, after "AAT C" insert --(Sequence No. 42)--.

At page 89, line 10, after "TGC" insert --(Sequence No. 43)--.

At page 89, line 11, after "CAT" insert --(Sequence No. 44)--

IN THE CLAIMS:

Please cancel claims 110, 116, 137, 138, 144, 145, 158, 171, 172, 173, 183, 197, 200, 201, 205-213.

Please amend the claims as follows:

95. (Amended) A method for electronic synthesis of an array of separately formed complex structures on a substrate, comprising the steps of:

providing a substrate having an array of controllable electrodes supported by the substrate,

providing first structures coupled to the electrodes, the structures having a blocked functional group,

providing a solution in contact with the array of electrodes,

applying a potential to selected electrodes where synthesis is to occur in order to cause deblocking of the first structure,

reacting a second structure with the deblocked first structure, and

repeating the steps of deblocking and reacting another structure to form the plurality of complex structures.

98. (Amended) The method of claim 97 wherein the polymer is a synthetic polymer.

99. (Amended) The method of claim 97 wherein the polymer is a biopolymer.

106. (Amended) The method of claim 95 wherein the first structure is a chemically reactive moiety.

108. (Amended) The method of claim 95 wherein the synthesis of the complex structures occurs without mechanical movement of electrodes.

132. (Amended) The method of claim 131 wherein the sequence of the complex structures in ~~of~~ the array is determined by selective activation of electrodes adjacent a common solution.

135. (Amended) The method of claim 95 wherein the electric field causes increased local concentration of reagents at the sites where the synthesis is to occur.

136. (Amended) The method of claim 95 wherein the solution contains a sodium phosphate buffer.

143. (Amended) A method according to claim 142, wherein said buffering solution is selected from the group consisting of: tris borate buffers, sodium chloride, sodium citrate buffers, and sodium phosphate buffers.

149. (Amended) A method according to claim 142, wherein said substrate is formed from at least one material selected from silicon, glass, ceramics, silicon dioxide and plastic.

150. (Amended) A method according to claim 142, wherein said array of electrodes comprises at least 64 electrodes.

157. (Amended) A method for electronically controlled synthesis of a plurality of complex structures on a substrate, comprising the steps of:

providing a substrate having a plurality of controllable electrodes supported by the substrate and covered with a permeable layer,

providing first structures coupled to the layer, the structures having a protected functional group,

providing a solution in contact with the array of electrodes supported by the substrate,

applying a potential to selected electrodes where synthesis is to occur,

reacting a second structure with the first structure, and

repeating the step of applying a potential and reacting a subsequent structure to form the complex structures, the synthesis of the array of structures occurring without mechanical movement.

161. (Amended) The method of claim 160 wherein the polymer is a synthetic polymer.

162. (Amended) The method of claim 160 wherein the polymer is a biopolymer.

169. (Amended) The method of claim 157 wherein the first structure is a chemically reactive moiety.

173. (Amended) The method of claim 157 wherein the layer couples the first structure to the electrode.

174. (Amended) The method of claim 157 wherein the layer comprises a mesh structure.

175. (Amended) The method of claim 157 wherein the layer comprises a porous structure.

176. (Amended) The method of claim 157 wherein the layer comprises a lawn structure.

177. (Amended) The method of claim 157 wherein the layer is a monolayer.

182. (Amended) The method of claim 157 wherein the layer is a permeation layer.

195. (Amended) The method of claim 157 wherein the sequence of the structures of the array ~~is~~ are determined by selective activation of electrodes adjacent a common solution.

198. (Amended) The method of claim 157 wherein the electric field causes increased local concentration of reagents at the sites where the synthesis is to occur.

199. (Amended) The method of claim 157 wherein the solution contains a sodium phosphate buffer.

REMARKS

Applicants wish to thank the Examiner for the courtesy of the in-person interview on August 27, 2001 with Dr. Sosnowski and the undersigned. In addition to the summary made on the PTOL-413, Applicants wish to note that the following references were specifically discussed: Southern USP 5,667,667, Hollis USP 5,653,939 and Fodor USP 5,445,934. Applicant disclosed the pendency of the litigation styled *Nanogen, Inc. v. Donald D. Montgomery and Combimatrix, Corp.*, and indicated that the '302 patent was involved in that litigation. A supplemental Information Disclosure Statement and Form SB/08A are enclosed. These materials further list all references cited in the Montgomery patents.

Applicants have amended the specification to insert the sequence information as required. In addition we are filing herewith a Statement Under 37 CFR §1.821(e) regarding the filing of the sequence in a parent case. Additionally, a number of amendments are made to the specification which had been requested by the Examiner in parent cases.

Applicants have reviewed the pending claims in detail in order to correct certain dependencies, to conform the claims more specifically to specification support and to eliminate issues in providing claims corresponding to Applicant's proposed counts. Claims 205-213 have been deleted as being directed to patentably distinct subject matter from the remaining claims. Applicant intends to pursue these claims in a continuation case. Finally, with the cancellation of claims, Dr. Sosnowski and Dr. Evans should be removed as named inventors on this application. A petition for their removal is being filed herewith. In addition, a new Declaration for inventors Heller and Tu will be submitted shortly.

On August 28, 2001, the day after the interview with the Examiner, U.S. Patent No. 6,280,595 issued. The '595 patent is styled as a continuation of the application which issued as the '302 patent. Applicant has designated certain claims from the '595 patent as corresponding to the proposed counts.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

LYON & LYON LLP

Dated: September 21, 2001

By: _____
David Murphy
Reg. No. 31,125

DBM/dnd
633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
(949) 567-2300 or (213) 489-1600

"Version with markings to show changes made"

In the Specification:

The following amendments have been made to the specification:

At page 10, line 25, delete "claimed".

At page 10, line 29, delete "claimed".

At page 12, line 17, delete "claimed" and insert therefor --disclosed--.

At page 12, line 23, delete "claimed" and insert therefor --disclosed--.

At page 19, line 15, delete "which was actually fabricated, addressed with oligonucleotides, and tested".

At page 19, line 25, delete "Figure 7 shows" and insert therefor --Fig. 7a and Fig. 7b show--.

At page 19, line 27, after "micro-location" insert --, Fig. 7a showing the addressable microlocations in a neutral condition and Fig. 7b showing the addressable microlocations in a charged state--.

At page 19, line 28, delete "Figure 8 shows" and insert therefor --Figs. 8a, 8b, 8c and 8d show--.

At page 19, line 30, after "SSO-C)" insert --, Fig. 8a showing a first microlocation (ML-1) being addressed, Fig. 8b showing a second microlocation (ML-2) being addressed, Figure 8c showing a third microlocation (ML-3) being addressed and Figure 8d showing the three microlocations after being addressed and assembled--.

At page 19, line 31, delete "Figure 9 shows" and insert therefor --Figs. 9a, 9b and 9c show--.

At page 20, line 2, after "capture sequences" insert --, Fig. 9a showing specific capture sequences on addressable microlocations, Fig. 9b showing specific and nonspecific DNA adjacent

the structure of Fig. 9a, and Fig. 9c showing hybridized material adjacent microlocations ML-1 and ML-3--.

At page 20, line 3, delete "Figure 10 shows" and insert therefor --Figs. 10a and 10b show--.

At page 20, line 4, after "hybridization process" insert --, Fig. 10a showing materials adjacent microlocation ML-3 and Fig. 10b showing materials adjacent microlocations ML-3 and ML-5--.

At page 20, line 5, delete "Figure 11 shows" and insert therefor --Figs. 11a, 11b and 11c show--.

At page 20, line 7, after "mutations" insert --, Fig. 11a showing uncharged addressable microlocations, Fig. 11b showing negatively charged microlocations and Fig. 11c showing negatively charged microlocations with material denatured from microlocation ML-3--.

At page 20, line 8, delete "Figure 12 shows" and insert therefor --Figs. 12a, 12b, 12c and 12d show--.

At page 20, line 11, after "process" insert --, Fig. 12a showing uncharged microlocations, Fig. 12b showing negatively charged microlocations, Fig. 12c showing uncharged microlocations with dye and Fig. 12d showing positively charged microlocations--.

At page 20, line 12, delete "Figure 13 shows" and insert therefor --Figs. 13a, 13b and 13c show--.

At page 20, line 13, after "device" insert --, Fig. 13a showing negatively charged addressable microlocations, Fig. 13b showing two opposed substrates, one substrate being that of Fig. 13a and the other being a sister device containing an attachment layer, and Fig. 13c showing two substrates, each of which has sequences bound to the microlocations--.

At page 20, line 14, delete "Figure 14 shows" and insert therefor --Figs. 14a, 14b, 14c, 14d, 14e, and 14f show--.

At page 20, line 15, after "oligonucleotides" insert --, Fig. 14a showing addressable microlocations with blocking groups, Fig. 14b showing addressable microlocations with blocking groups in combination with a deblocking group, Fig. 14c showing blocked and deblocked addressable microlocations in the presence of monomer C, Fig. 14d showing addressable microlocations in combination with a deblocking group, Fig. 14e showing deblocked cites on microlocation ML-2 in the presence of monomer A and Fig. 14f showing microlocations with blocking groups on the terminal ends of sequences--.

At page 39, line 15, delete "Figure 7" and insert therefor --Figs. 7a and 7b--.

At page 39, line 21, delete "Figure 8" and insert therefor --Figs. 8a through 8d

At page 42, line 1, delete "claimed".

At page 42, line 18, delete "claimed" and insert therefor --disclosed--.

At page 43, line 12, delete "Figure 8" and insert therefor --Figs. 8a through 8d--.

At page 44, line 27, delete "Figure 9" and insert therefore --Figs. 9a through 9c--.

At page 45, line 24, delete "Figure 10" and insert therefor --Figs. 10a and 10b--.

At page 46, line 4, delete "claimed" and insert therefor --disclosed--.

At page 46, line 8, delete "Figure 11" and insert therefor --Figs. 11a through 11c--.

At page 49, line 1, delete "Figure 12" and insert therefor --Figs. 12a through 12d--.

At page 51, line 7, delete "Figure 13" and insert therefor --Figs. 13a through 13c--.

At page 54, line 12, "Figure 14" and insert therefor --Figs. 14a through 14f--.

At page 60, line 7, after "TCU" insert --(Sequence No. 1)--.

At page 60, line 8, after "AAU" insert --(Sequence No. 2)--.

At page 60, line 9, after "CTG U" insert --(Sequence No. 3)--.

At page 60, line 10, after "GU" insert --(Sequence No. 4)--.

At page 60, line 11, after "CU" insert --(Sequence No. 5)--.

At page 60, line 12, after "AGU" insert --(Sequence No. 6)--.

At page 60, line 13, after "GU" insert --(Sequence No. 7)--.

At page 60, line 14, after "ACU" insert --(Sequence No. 8)--.

At page 60, line 15, after "GAC U" insert --(Sequence No. 9)--.

At page 60, line 16, after "TU" insert --(Sequence No. 10)--.

At page 60, line 17, after "CU" insert --(Sequence No. 11)--.

At page 60, line 18, after "TU" insert --(Sequence No. 12)--.

At page 61, line 2, after "AT" insert --(Sequence No. 13)--.

At page 61, line 3, after "AGG" insert --(Sequence No. 14)--.

At page 61, line 4, after "CTC" insert --(Sequence No. 15)--.

At page 61, line 5, after "TTT T" insert --(Sequence No. 16)--.

At page 61, line 7, after "TAG" insert --(Sequence No. 17)--.

At page 61, line 8, after "ACT C" insert --(Sequence No. 18)--.

At page 61, line 9, after "TAC G" insert --(Sequence No. 19)--.

At page 61, line 10, after "AC" insert --(Sequence No. 20)--.

At page 61, line 11, after "CAT C" insert --(Sequence No. 21)--.

At page 61, line 12, after "AG" insert --(Sequence No. 22)--.

At page 61, line 13, after "GAA" insert --(Sequence No. 23)--.

At page 61, line 14, after "GGA A" insert --(Sequence No. 24)--.

At page 61, line 15, after "AAC A" insert --(Sequence No. 25)--.

At page 61, line 16, after "GAT G" insert --(Sequence No. 26)--.

At page 70, line 8, delete "the".

At page 71, line 10, delete "silica" and insert therefor --silicon--.

At page 71, line 28, delete ". Then" and insert therefor --, and then--

At page 75, line 33, after "micro-location" insert --(Sequence No. 27)--.

At page 76, line 2, after "micro-location" insert --(Sequence No. 28)--.

At page 76, line 5, after "(TR)" insert --(Sequence No. 29)--.

At page 76, line 6, after "(TR)" insert --(Sequence No. 30)--.

At page 76, line 7, after "(TR)" insert --(Sequence No. 31)--.

At page 78, line 12, after "GAU" insert --(Sequence No. 32)--.

At page 78, line 14, after "GA" insert --(Sequence No. 33)--.

At page 78, line 15, after "CCA C" insert --(Sequence No. 34)--.

At page 78, line 16, after "CCA C" insert --(Sequence No. 35)--.

At page 78, line 17, after "CCA C" insert --(Sequence No. 36)--.

At page 78, line 18, after "CCG C" insert --(Sequence No. 37)--.

At page 78, line 19, after "ACG C" insert --(Sequence No. 38)--.

At page 89, line 4, after "CAG U" insert --(Sequence No. 39)--.

At page 89, line 5, after "GTG U" insert --(Sequence No. 40)--.

At page 89, line 7, after "ACC G" insert --(Sequence No. 41)--.

At page 89, line 9, after "AAT C" insert --(Sequence No. 42)--.

At page 89, line 10, after "TGC" insert --(Sequence No. 43)--.

At page 89, line 11, after "CAT" insert --(Sequence No. 44)--

<u>In the Claims</u>:

Claims 110, 116, 137, 138, 144, 145, 158, 171, 172, 173, 183, 197, 200, 201, 205-213 have been cancelled.

The claims have been amended as follows:

95. (Amended) A method for electronic synthesis of <u>an array of separately formed</u> ~~a plurality of~~ complex structures on a substrate, comprising the steps of:

providing a substrate having ~~a plurality~~ <u>an array</u> of controllable electrodes supported by the substrate,

providing first structures coupled to the electrodes, the structures having a blocked functional group,

providing a solution in contact with the array of electrodes,

applying a potential to selected electrodes where synthesis is to occur in order to cause deblocking of the first structure,

reacting a second structure with the deblocked first structure, and

repeating the steps of deblocking and reacting another structure to form the plurality of complex structures.

98. (Amended) The method of claim ~~95~~ <u>97</u> wherein the polymer is a synthetic polymer.

99. (Amended) The method of claim ~~95~~ <u>97</u> wherein the polymer is a biopolymer.

106. (Amended) The method of claim 95 wherein the first structure is a chemically reactive <u>moiety</u> ~~moeity~~.

108. (Amended) The method of claim 95 wherein the synthesis of the ~~plurality of~~ complex structures occurs without mechanical movement of electrodes.

132. (Amended) The method of claim ~~95~~ 131 wherein the sequence of the complex structures in ~~of~~ the array is determined by selective activation of electrodes adjacent a common solution.

135. (Amended) The method of claim 95 wherein the electric field causes increased local concentration of reagents at the sites where the ~~sub-unit~~ synthesis is to occur ~~be coupled~~.

136. (Amended) The method of claim 95 wherein the solution contains a sodium phosphate buffer.

143. (Amended) A method according to claim 142, wherein said buffering solution is selected from the group consisting of: tris borate buffers, sodium chloride, sodium citrate buffers, and sodium phosphate buffers.

149. (Amended) A method according to claim 142, wherein said substrate is formed from at least one material selected from silicon, ~~semiconductors,~~ glass, ceramics, silicon dioxide and plastic~~polymers~~.

150. (Amended) A method according to claim 142, wherein said array of electrodes comprises at least ~~100~~ 64 electrodes.

157. (Amended) A method for electronically controlled synthesis of a plurality of complex structures on a substrate, comprising the steps of:

providing a substrate having a plurality of controllable electrodes supported by the substrate and covered with a permeable ~~non-insulating~~ layer,

providing first structures coupled to the layer ~~electrodes~~, the structures having a protected functional group,

providing a solution in contact with the array of electrodes supported by the substrate,

applying a potential to selected electrodes where synthesis is to occur,

reacting a second structure with the first structure, and

repeating the step of applying a potential and reacting a subsequent structure to form the complex structures, the synthesis of the array of structures occurring without mechanical movement.

161. (Amended) The method of claim ~~157~~ 160 wherein the polymer is a synthetic polymer.

162. (Amended) The method of claim ~~157~~ 160 wherein the polymer is a biopolymer.

169. (Amended) The method of claim 157 wherein the first structure is a chemically reactive moiety ~~moeity~~.

173. (Amended) The method of claim ~~172~~ 157 wherein the layer couples the first structure to the electrode.

174. (Amended) The method of claim ~~172~~ 157 wherein the layer comprises a mesh structure.

175. (Amended) The method of claim ~~172~~ 157 wherein the layer comprises a porous structure.

176. (Amended) The method of claim ~~172~~ 157 wherein the layer comprises a lawn structure.

177. (Amended) The method of claim ~~172~~ 157 wherein the layer is a monolayer.

182. (Amended) The method of claim ~~172~~ 157 wherein the layer is a permeation layer.

195. (Amended) The method of claim 157 wherein the sequence of the structures of the array ~~is~~ are determined by selective activation of electrodes adjacent a common solution.

198. (Amended) The method of claim 157 wherein the electric field causes increased local concentration of reagents at the sites where the ~~sub-unit~~ synthesis is to occur ~~be coupled~~.

199. (Amended) The method of claim 157 wherein the solution contains a sodium phosphate buffer.